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| 10/566,844 | 02/01/2006 | Dirk Beher | T1632Y | 9399 |

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| EXAMINER | |
|---|---|
| RAO, SAVITHA M | |
| ART UNIT | PAPER NUMBER |
| 1614 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/566,844 | BEHER ET AL. | |
| | Examiner | Art Unit | |
| | SAVITHA RAO | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5-7,9 and 11-13* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7, 9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 5-7, 9 and 11-13 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 02/09/2009 is acknowledged. Claims 5, 6, 11 and 13 are amended and claims 1, 3-4 and 8, are cancelled. Claims under consideration in the instant office action are claims 5-7, 9 and 11. Claims 12-13 are withdrawn from consideration as being drawn to a non-elected invention.

Applicants' arguments, filed 02/09/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

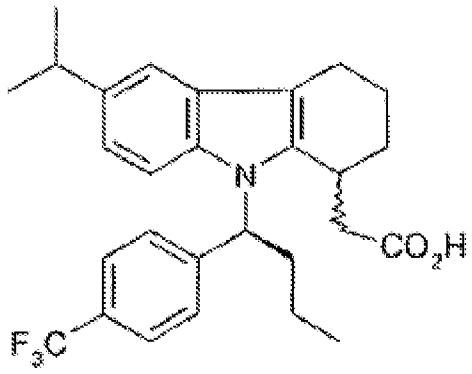
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

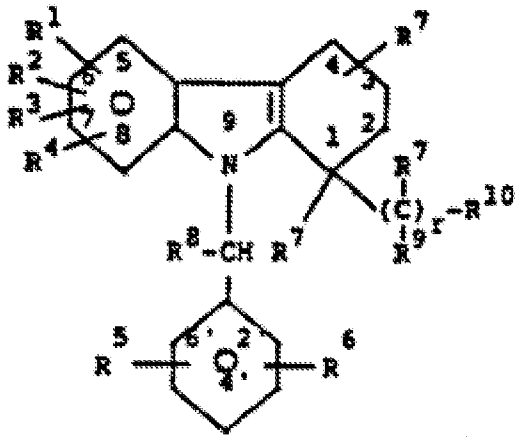
Claims 5-7, 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford -Hutchinson (EP 0307077, referenced in instant IDS) as evidenced by Patani et al. (Chemical Reviews, 1996, vol. 96 (8), pages 3147-3176) in view of Watanabe (US 6,514,984)

Instant claims are drawn towards the following compound (example 3)

**EXAMPLE 13**



Ford-Hutchinson teaches compounds of formula (I) shown below (page 4, lines 25-26 and claim 1). Among various substituents taught for each of the R variable below, the following listed substituent read on the instantly claimed compound



I

Wherein $R^1$= alkyl or alkenyl having 1-6 carbon atoms;

$R^2$, $R^3$ and $R^4$ = H,

$R^6$ is - $(CH)_n$ M where n = 0 and M is CF3

$R^5$ is H

$R^7$ is H

$R^8$ is H or alkyl of 1-6 carbon atoms

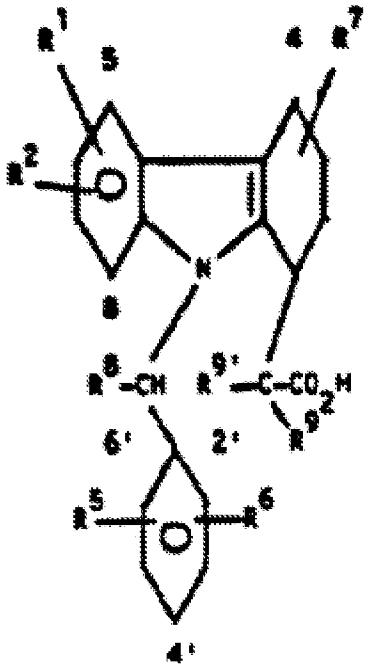
$R^9$ is H

$R^{10}$ is COOH

Accordingly, the instantly claimed compound is entirely encompassed by the generic compound I taught by Ford- Hutchinson above

Ford-Hutchinson additionally teaches tetahydrocarbazole alkanoic acid compounds of general formula shown below (page 8, line 10-30 and page 10, lines 1 and 11)

**Tetrahydrocarbazole Alkanoic Acids**



| Compound | $R^1$ | $R^2$ | $R^5$ | $R^6$ | $R^9$, $R^{9'}$ | $R^7$ | $R^8$ |
|---|---|---|---|---|---|---|---|
| 24 (Ex. 24) | 6-$CH(Me)_2$ | H | 4'-Cl | H | H,H | H | H |

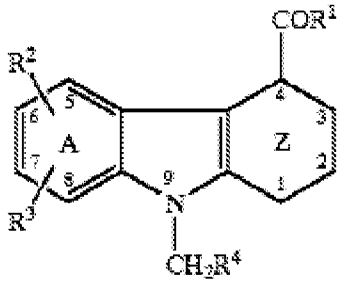
The only difference between the instantly claimed compound example 13 (page 55 of instant disclosure) and the compound taught by Ford-Hutchinson above are the substitution of 4' Chlorine instead of 4' trifluoromethyl group substitution in the position 4 of the N-$CH_2$-phenyl group and where R8 is H instead of propyl group of the instantly claimed compound. The generic formula teaches the substitution of $CF_3$ in position 4 of the N-$CH_2$-phenyl group and the substitution of alkyl group of 1-6 carbon at position $R^8$. Accordingly one of ordinary skill in the medicinal chemistry art would be motivated to synthesize the instantly claimed compound. Additionally, Patani et al is used here for evidence that the Cl group and $CF_3$ group are bioisosteres and one can be substituted by the other. Patani teaches that halogens have been replaced by electron-withdrawing groups such as a cyano or trifluoromethyl groups and illustrates such a nonclassical replacement of halogen in a structure activity relationship study of cholesystokinin-A (CCK-A) receptor antagonists. CCK –A receptor antagonists have been proposed as potentially useful in the treatment of appetite disorders, abnormalities of gastric motility etc. As illustrated in Table 52 replacement of Cl with nonclassical bioisosteres such as CN or $CF_3$ resulted in retention of antagonistic activity at the CCK-A receptor (page 3172, section 6, Halogen Bioisosteres

Ford-Hutchinson does not teach the use of the compounds of his invention in a

composition.

However, Watanabe teaches a method for the prevention and treatment of Alzheimer's disease by administering to a human in need thereof an effective amount of a substituted tricyclic secretory phospholipase A2 (sPLA2) inhibitor (abstract). Watanabe teaches carbazole compounds of formula (XXX) below (col.10, lines 11-55)

(XXX)




Where $R^1$ is –NHNH2 or –NH2

$R^2$ is either hydroxy or alkoxy

$R^3$ is H

$R^4$ is –(C1-C4) alkyl phenyl

A is phenyl

Z is cyclohexenyl

Watanabe additionally teaches formulations comprising substituted tricyclic compounds of his invention which could be compositions suitable for internal administration together with a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration (col.55, lines 49-57).

Accordingly, it would have been *prima facie* obvious to the ordinarily skilled medicinal chemist to synthesize the instantly claimed compounds and compositions.

Instantly claimed compound is encompassed by the generic compound taught by Ford-Hutchinson and Ford-Hutchison additionally teaches a compound structurally similar to the instantly claimed compound except for the chloro substitution instead of $CF_3$ and the H instead of Propyl group at the R8 position of the compound taught by Ford-Hutchinson. Watanabe teaches structurally similar compounds useful for the treatment of Alzheimer's and teaches pharmaceutical compositions comprising them. Accordingly one of ordinary skill in medicinal chemistry art would be motivated to try out the range of substituents taught by Ford-Hutchinson to arrive at the instantly claimed compounds. Watanabe provides additional motivation as structurally similar compounds and compositions have been shown to be used for treatment of Alzheimer's disease. An ordinarily skilled artisan would be imbued with a reasonable expectation of success that compounds and compositions synthesized as taught by Ford-Hutchinson would find potential use for treatment of Alzheimers disease. It is to be noted that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and/or similar utilities. "An obviousness rejection based on similarity in chemical structure and/or function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

**Response to applicant's arguments filed on 07/31/2008:**

Applicant traverses the above rejection with the following arguments:

a. The fact that a claimed .. subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness and one skilled in the art must be motivated to select the claimed subgenus from the disclosed art genus. As such the compounds are not rendered obvious by Ford-Hutchinson.

b. Examiner is engaging in impermissible hindsight with knowledge of their present invention to select $CF_3$ out of many other possibilities.

c. Patani demonstrates that substitution of $CF_3$ to Cl behaves differently depending on the specific chemical compounds and target.

d. obvious to try is not the proper standard to conduct an obviousness determination

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

In response to applicants argument that the fact that subgenus is encompassed by a prior art genus is not sufficient to establish a prima facie case of obviousness and to the argument that obvious to try is not the proper standard to conduct an obviousness determination, it is noted that A reference is analyzed using its broadest teachings. MPEP 2123 [R-5]. It must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the

improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an automaton." Id. at 1742. Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement". In the instant case, the instantly claimed compound is explicitly suggested by Ford-Hutchinson within a finite list of compounds encompassed by the generic compounds and the exemplified compounds and as such renders the instantly claimed compound and composition obvious. It is to be noted that the instantly claimed compounds are fully rejected as being obvious over the teachings of Ford-Hutchinson. Patani and Watanbe references are brought into the rejections as a supporting document.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments that Patani demonstrates that substitution of $CF_3$ to Cl behaves differently depending on the specific chemical compounds and target, Examiner agrees with the applicant that Patani teaches the decrease in potency of uridine phosphorylase inhibition by 5-benzyluracil by substitution of chlorine with CN or CF3 and it is true that substitution of CF3 to Cl behaves differently depending on the specific chemical compounds and target. However, Patani also teaches that the replacement with nonclassical bioisosteres of the halogens in the benzdiazepines resulted in retention of antagonistic activity at the CCK-A receptor which is ample motivation for an ordinarily skilled artisan in medicinal chemistry art to modify compounds with halogen moiety with bioisosteres such as CN or CF3 in an effort to obtain compounds with similar activity but provide other advantages such as increase in metabolic stability, change in basicity of the compound which increases better membrane permeability and subsequently the bioavailability and increase the binding affinity of a compound

## *Conclusion*

**Claims 1-7, 9 and 11-13 are rejected. No claims are allowed**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614